REMARKS

Formalities

The Examiner states that copies of the PCT/GB01/03290 and GB0017990.3 have not been submitted. Please note that the instant application is a continuation application of US 09/939,471, which in turn is continuation in part of PCT/GB01/03290. Enclosed is a copy of Office Action Summary mailed by Examiner Salimi for US 09/939,471 dated January 28, 2003 indicating that all certified copies of the priority documents have been received.

Claims 37 and 38 were objected because they were identical. They have now been amended.

Claim Rejections 35 USC §112

Claims 39-40 have been rejected under 35 U.S.C. 112, second paragraph. The Examiner notes that antecedent bases for claims 39 and 40 are incorrect.

Claim 38 from which claims 39 and 40 depend has been amended to correct the defect in the antecedent bases.

Claim Rejections – 35 USC §112

Claims 36-53 have been rejected under 35 U.S.C. 112, first paragraph, because according to the Examiner, the specification, while being enabling for HPV6b E1 and HPV 11 E2 which are codon optimized or modified to be utilized in an induction of antibody immune response (treatment only), does not reasonably provide enablement for any and all "codon usage pattern" of all HPVs genes which has been rearranged to be expressed to treat and/or prevent infection caused by HPVs.

First, Applicants agree with the Examiner that to be enabling the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue" experimentation. Wright, 999 F.2d at 1561, 27 USPQ2d at 1513. However, Applicants respectfully do not agree with the Examiner that specification does not provide a "credible teaching" as alleged by the Examiner. Credible teaching has nothing to do with enablement. USC 112 first paragraph (enablement) imposes two basic requirements: (1) how to make, and (2) how to use. The disclosure of the specification adequately complies with the requirements. For example, as disclosed on page 16 lines 19-20 of the specification, the method of claimed invention uses a Visual Basic program called Calcgene, written by R. S. Hale and G Thompson (Protein Expression and Purification Vol. 12 pp.185-188 (1998)), and was already available in the public domain as of the filing date. The methods claimed in the present invention are generally applicable to all HPV genes, particularly in view of the amendments that now limit the claims to the particular codon usage coefficient of greater than 0.5 but less than 1. Despite the natural variation between HPV genes, the method of the present invention provides generally applicable means of increasing expression of any given HPV protein by altering the natural gene sequence to match the natural codon availability in the cell, and it is not specific to any one gene. The variation between different HPV genes makes no difference to the effectiveness of the method, as the natural sequence of each gene is taken, and then optimized to reflect the codon availability i.e. the tRNA availability in the cell - which is the same for whichever HPV gene is being optimized. The Codon Adaptation Index (CAI) is a measure of codon bias - it is the geometric mean of the codon preferences. Genes with low CAIs may be expected to be expressed poorly would benefit from the optimization. The method of the present invention is predicted to work with any HPV gene, as HPV genes have a low codon adaptation index (~2.7-3.5), therefore optimizing the codons of these genes according to the methods of the present invention is likely to improve their expression.

Applicants have demonstrated in the specification rearrangement of papillomavirus sequences for E1 polynucleotide of HPV6b E1, and HPV11 E2 only to exemplify the technique claimed, but not as a limitation of the technique.

The Examiner raises such issues as toxicity, transformation and reversion of rearranged protein to the wild type. However, the toxicity issue is certainly of concern to the FDA, but not with patentability. Almost every drug is associated with some adverse side effects, and FDA will determine acceptable level of toxicity in a drug. The issue of transformation is also irrelevant here because the present invention is concerned with a method of expression of HPV polypeptides, or a method of preventing or treating HPV infection. We need not worry about the reversion to the wild type because Applicants are only seeking transient expression to elicit immune response or expression. In conclusion, using Calcgene, a skilled artisan can practice the claimed invention without undue experimentation.

Claim Rejections 35 USC §112

Claims 36-53 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner states, inter alia,

> *In the instant disclosure, Applicants have only disclosed the optimized sequence of HPV6b E1, HPV11 E2 only. No other sequences, which are "optimized", were disclosed. The specification does not set forth the metes and bounds of that encompasses of "codon usage pattern" of "highly expressed mammalian genes having", and there is not enough information about it in literature either to guide the one of ordinary skill in the art to predict the undisclosed regions. Therefore, a written description of the other sequences that should be utilized in the methods should be disclosed to overcome this rejection...*

As stated earlier in traversing lack of enablement rejection, the instant invention relates to the use of known algorithm (computer program) to generate optimal codons. The method is described in a Visual Basic program called Calcgene, written by R. S. Hale and G Thompson (Protein Expression and Purification Vol. 12 pp.185-188 (1998)). Thus once the starting HPV sequences are selected for optimization, the optimized codons are readily generated by the computer program. It is submitted that

written description requirement does not require to reproduce information known to those skilled in the art.

Claim Rejections 35 USC §102

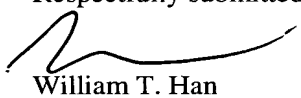
Claims 36-43, and 47-50 are rejected under 35 U.S.C. 102(e) as being anticipated by Neeper at al (WO 01/14416 A2).

Independent claims 36 and 47 have now been amended to recite the limitation of greater than 0.5 but less than 1. Support can be found on page 6, line 16. Such amendment should obviate 35 USC 102 rejection raised by the Examiner.

This reply is intended to distinctly and specifically point out presumed errors in the Examiner's Action, to respond to every ground of objection and rejection, and to advance this case to allowance.

In view of the above remarks, reconsideration of this application is requested. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned agent at the number below.

Respectfully submitted,



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